Cyclopentasiloxane, decamethyl-: Human health tier II assessment

30 June 2017

CAS Number: 541-02-6

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

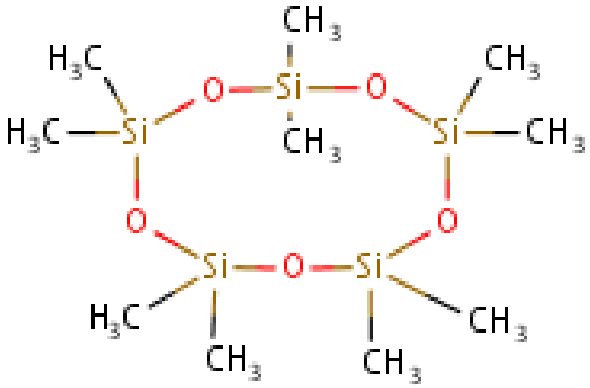
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	dimethylsiloxane pentamer cyclic dimethylsiloxane pentamer polydimethylsiloxane D5 cyclosiloxane cyclomethicone 5
Structural Formula	
Molecular Formula	C10H30O5Si5
Molecular Weight (g/mol)	370.78
Appearance and Odour (where available)	colourless to pale yellow clear oily liquid
SMILES	C[Si]1(C)O[Si](C)(C)O[Si](C)(C)O[Si](C)(C)O[Si](C)(C)O1

Import, Manufacture and Use

Australian

The chemical was reported under previous mandatory and/or voluntary calls for information. The total volume introduced into Australia was low, and the identified uses were cosmetic and site-limited.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB) and the US Household Products database; the International Fragrance Association (IFRA) Survey Transparency List (IFRA, 2011); and various international assessments (Government of Canada, 2008; EA, 2009; Johnson et al., 2011; HSE, 2015).

The chemical has reported cosmetic uses, including:

- in fragrance compounds;
- as an emollient in skin conditioning agents, including in sunscreens at a concentration of <20 % and in other products at a concentration of 6–40 %;
- in hair conditioning agents, at a concentration of 1–100 %;
- in anti-perspirants at a concentration of 5–60 %; and
- as a solvent (e.g. lubricant and foam control agent in hair sprays).

The chemical has reported domestic uses, including in:

- car waxes and polishes, at a concentration of 1–60 %;
- pre-wash stain removers; and
- cleaning and washing agents.

The chemical has reported commercial uses, including in:

- dry cleaning agents;
- reprographic agents;
- construction materials (e.g. adhesives, binding agents, paints, lacquers and varnishes);
- manufacture of textiles (e.g. leather, fur); and
- manufacture of electrical, electronic or optical equipment.

The chemical has reported site-limited uses, including:

- as a fuel additive; and
- as an intermediate in silicone fluid and elastomer production.

The chemical has reported non-industrial uses, including in:

- non-agricultural pesticides;
- breast implants; and
- medical adhesive and pharmaceutical formulation.

Restrictions

Australian

No known restrictions have been identified.

International

The United Kingdom had submitted to the European Chemicals Agency (ECHA) an Annex XV dossier proposing to restrict the use concentration of the chemical in wash-off personal care products at ≥0.1 %. The basis of the restriction is not on human health grounds but on environmental concerns, with the chemical having met the Annex XIII criteria for being very persistent very bioaccumulative (vPvB) and being a persistent, bioaccumulative and toxic (PBT)/vPvB containing substance as octamethylcyclotetrasiloxane may be present as an impurity. The ECHA Committee for Risk Assessment (RAC) and Committee for Socio-economic Analysis (SEAC) recently released their Opinion supporting the proposal.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific international exposure standards are available.

Health Hazard Information

The chemical, decamethylcyclopentasiloxane, is a component of cyclomethicone (cyclosiloxanes, dimethyl; CAS No. 69430-24-6), which is a mixture of cyclic dimethyl polysiloxane compounds consisting of 3–7 [–Si(CH_3)$_2$O–]x base units. Cyclomethicone is widely used in cosmetics and is predominantly composed of octamethylcyclotetrasiloxane and decamethylcyclopentasiloxane (Government of Canada, 2008; SCCS, 2010; Johnson et al., 2011).

Toxicokinetics

Based on the available data from in vivo and in vitro studies, absorption of the chemical is highest with oral exposure, followed by inhalation and then dermal exposure. The chemical is metabolised by demethylation and Si–O bond hydrolysis. It is excreted unchanged or as metabolites via exhaled air and in faeces and urine.

In vivo

In a dermal absorption study in healthy adult volunteers (n = 3/sex), 1.4 g or 1.0 g total of radiolabelled chemical was applied once to the axillae (arm pits) of males and females, respectively, and chemical levels were assessed in blood, plasma and exhaled air for up to 24 hours. There was no significant difference in absorption between males and females, both being approximately 0.05 %. Chemical levels in blood, plasma and exhaled air were above baseline measures at all time points assessed. The maximum plasma chemical level was 1.22 ng/g at one hour after exposure, reducing to 0.61 ng/g at six hours after exposure. Exhaled chemical levels were higher than expected based on blood levels, and reached a maximum by one hour post exposure (SCCS, 2010; Johnson et al., 2011; Dekant & Klaunig, 2016; REACH).

In an inhalation study, human volunteers (n = 3 males and 2 females) were exposed (via a mouth piece) to the chemical vapour once, at 10 ppm (equivalent to approximately 160 mg/m^3) for one hour during a mixed rest and exercise regimen. In exhaled air, steady state concentrations of 7–10 ppm were achieved rapidly and declined to 1 ppm within 20 minutes of exposure ending. The plasma chemical concentration increased from 0.15–3.3 µg/L at baseline to 31–70 µg/L at the end of the exposure period, and back to baseline levels within 24 hours of exposure ending (Dekant & Klaunig, 2016).

In a toxicokinetics study conducted according to EPA OTS 798.7485, Fischer 344 (F344) rats (n = 20 males and 48 females) were exposed to radiolabelled chemical once by oral gavage at 1000 mg/kg bw and assessed for up to 168 hours. The chemical was administered neat (females only), or using corn oil (males and females) or simethicone fluid (females only) as the vehicle. Total absorption from corn oil was 20–22 %, and systemic availability was highest in female rats that received the chemical in corn oil, followed by neat chemical and lowest with simethicone vehicle. The chemical was distributed to tissues such as bone marrow, liver, kidneys and adipose tissue. Approximately 60–80 % of the administered chemical was excreted unchanged in faeces; 20 % of the administered chemical was excreted as polar metabolites in urine; and 50 % of the systemically available chemical was excreted unchanged in exhaled air. Metabolites were also detected in blood. The elimination half-life in blood ranged from 45 to 242 hours (Dekant & Klaunig, 2016; REACH).

Urinary metabolites of the chemical were investigated in female F344 rats (n = 2/dose) following a single oral exposure to radiolabelled chemical at two doses (7.6 mg and 8.7 mg of a solution containing 17.377 mCi/mmol). The major metabolites identified in urine were dimethylsilanediol and methylsilanetriol, and at least five minor metabolites were also identified. Demethylation at silicon-methyl bonds was determined to be one metabolic pathway leading to their formation (Varaprath et al., 2003; REACH).

Adipose tissue metabolites were investigated in female F344 rats (n = 6) following a single oral exposure to the radiolabelled chemical at 1000 mg/kg bw. The chemical was present in adipose tissue as the parent and as the metabolite nonamethylcyclopentasiloxanol, formed by oxidative demethylation (REACH).

In a dermal absorption study conducted similarly to the Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 427, SD rats (n = 6 males and 5 females) were dermally exposed to radiolabelled chemical (20 µL, containing 20 µCi radioactivity) to clipped skin for 24 hours. The dose site was then washed and wrapped (non-occlusive) for another 72 hours. It was reported that 85 % of the chemical volatilised from the skin surface, with 0.35 % remaining at the dose site at 96 hours. The total amount of chemical absorbed was determined to be 0.80 ± 0.62 % at 96 hours, and there were minimal amounts of the chemical distributed in the tissues (highest in liver and fat) (SCCS, 2010; Dekant & Klaunig, 2016; REACH).

In another dermal absorption study (conducted similarly to EPA OTS 870.7600), female F344 rats (n = 18) were dermally exposed to radiolabelled chemical for six or 24 hours. The dose site was then washed, with some animals euthanised for analysis at six and 24 hours, or the dose site wrapped (non-occlusively) for up to a total of 168 hours' exposure. It was reported that the majority of the chemical evaporated from the skin surface by six hours. The amount of chemical systemically available was determined to be 0.243 ± 0.0259 % at 24 hours and 0.089 ± 0.0302 % at 168 hours (SCCS, 2010; REACH).

In a nose-only inhalation study, F344 rats (n = 48 female and 3 male) were exposed once to radiolabelled chemical vapour at 160 ppm (equivalent to approximately 2500 mg/m^3) for six hours and blood, plasma, tissues, exhaled air, urine or faeces were assessed at different time points during exposure and up to 168 hours post-exposure. The body burden (total chemical amount present in the animal) was approximately 3 % of the administered dose. The maximum plasma concentration was 3.39 µg/mL which was detected at the start of exposure. The elimination half-life was determined to be 58.9 hours (SCCS, 2010; REACH).

In a nose-only inhalation study conducted similarly to OECD TG 417, F344 rats (n = 53/sex/dose) were exposed once to the radiolabelled chemical vapour at 7 or 160 ppm (equivalent to approximately 110 and 2500 mg/m^3) for six hours. The absorbed fraction was approximately 2 % of the dose, irrespective of sex or exposure concentration. The chemical distributed (in descending order of concentration) to the small and large intestines, stomach, thyroid (males only), lungs and adrenal glands in animals exposed to the low concentration; and to the small and large intestines, stomach, lungs, adrenal glands and liver in animals exposed to the high concentration. The chemical was also detected in plasma, whole blood, adipose tissue, testes, uterus and vagina. Expiration of the chemical was 3–4 times higher in males than in females, irrespective of the exposure concentration. The chemical was excreted unchanged in the faeces and as metabolites in the urine (Johnson et al., 2011; Dekant & Klaunig, 2016; REACH).

In another nose-only inhalation study, F344 rats were exposed to the chemical vapour at 160 ppm (equivalent to approximately 2500 mg/m^3) for six hours per day for 14 days, and then once to the radiolabelled chemical at 160 ppm for six hours on day 15. The absorbed fraction was approximately 9 % of the dose. The chemical was distributed to the small and large intestines, lungs, adrenal glands and fat. Maximum tissue concentrations were generally achieved by three hours post-exposure. Elimination of the chemical from adipose tissue was slower than from other tissues. The major routes of excretion were exhaled air (45–50 %), faeces (16 %) and urine (12 %). The chemical was excreted unchanged in the faeces and as various metabolites (demethylated or non-demethylated) in the urine (SCCS, 2010; Dekant & Klaunig, 2016; REACH).

Based on the well-characterised toxicokinetics data available for the chemical, physiologically-based pharmacokinetic modelling (PBPK) was used to explain its metabolism. The chemical is volatile and, therefore, elimination of free chemical from the venous circulation in the lungs can occur readily by exhalation. The chemical also volatilises during skin exposure, and any remaining in the skin following dermal exposure continues to evaporate after migrating back to the skin surface. The chemical has a high hepatic clearance, with 60–90 % of free chemical removed by first pass metabolism in the liver. The chemical is lipophilic, partitioning to the lipid compartments of the body slowly following exposure. Dermal or inhalation exposure results in absorption of free chemical, whereas absorption following oral exposure most likely occurs via interaction with chylomicrons or other lipid transport systems. Overall, these factors act to prevent significant bioaccumulation of the chemical (SCCS, 2011; Dekant & Klaunig, 2016).

In vitro

In a dermal absorption study conducted similarly to OECD TG 428, intact human abdominal skin (n = 3/treatment regimen) was exposed to radiolabelled (6 µCi) chemical, either neat or as a formulation in generic antiperspirant, for 24 hours before the skin was washed. The majority (approximately 90 %) of the chemical evaporated from the skin. The amount of chemical absorbed was similar for both treatment types and measured to be 0.040 ± 0.007 % and 0.022 ± 0.005 % for neat and formulated chemical, respectively (SCCS, 2010; Johnson et al., 2011; REACH).

In another dermal absorption study conducted similarly to OECD TG 428, skin from Sprague Dawley (SD) rats (n = 9 males and 8 females) was exposed to radiolabelled (12 µCi) chemical for 24 hours before being washed. The majority of the chemical volatilised from the skin, with 0.67 % and 1.19 % of the applied dose remaining in the skin in males and females, respectively. The amount of chemical absorbed was 1.08 % and 1.54 % in males and females, respectively (SCCS, 2010; REACH).

Acute Toxicity

Oral

Based on the available data, the chemical has low acute oral toxicity.

In an acute oral toxicity study (similar to OECD TG 401), the median lethal dose (LD50) in Wistar rats was >4800 mg/kg bw (Government of Canada, 2008; SCCS, 2010; Johnson et al., 2011). In addition, other LD50 values were reported as >61 440 mg/kg bw in male Wistar rats, >20 000 mg/kg bw in SD rats and >24 134 mg/kg bw in rats (strain not specified) (REACH; RTECS).

Dermal

Based on the available data, the chemical has low acute dermal toxicity.

The reported dermal LD50 values are >2000 mg/kg bw in New Zealand White (NZW) rabbits; >15 360 mg/kg bw in NZW rabbits; and >2400 mg/kg bw in rats (strain not specified) (REACH).

Inhalation

Based on the available data, the chemical has low acute inhalation toxicity.

In an acute inhalation toxicity study conducted according to OECD TG 403, the median lethal concentration (LC50) was 8.67 mg/L (560 ppm) in F344 rats exposed (nose-only) to the aerosolised chemical for four hours. Observed sub-lethal effects included rigid gait, hunched posture, ruffled fur, restlessness and tachypnoea (rapid breathing) (SCCS, 2010; Johnson et al., 2011; REACH).

In another acute inhalation toxicity study (OECD TG 403) in Wistar rats, the LC50 was reported to be >6.72 mg/L (>545 ppm) following a single whole body inhalation exposure for four hours. No mortality or overt signs of toxicity were noted (SCCS, 2010; REACH).

Corrosion / Irritation

Respiratory Irritation

Based on the available data from repeated inhalation toxicity studies (see **Repeat dose toxicity: Inhalation** and **Reproductive and developmental toxicity** sections), the chemical may be a mild respiratory irritant.

In several repeated dose inhalation toxicity studies (according or similar to OECD TG 412 or 413), F344 or SD rats exposed (nose only or whole body) to the chemical for 28 or 90 days showed increased incidence and severity of nasal cavity goblet cell (mucus-producing cells) proliferation and/or minimal to light lung interstitial inflammation. Effects were generally reversed after two or four week recovery periods, when there was no chemical exposure. These local morphological changes were considered to be of little or no relevance to human exposure (Government of Canada, 2008; EA, 2009; SCCS, 2010; Johnson et al., 2011; Danish EPA, 2014; Dekant & Klaunig, 2016; HSDB; REACH).

In a two-generation combined reproductive toxicity (according to EPA OPPTS 870.3800) and developmental neurotoxicity (according to EPA OPPTS 83-6) study, it was reported that parental (F0) and offspring (F1) SD rats exposed (whole body) to the chemical vapour had significantly increased incidence of pulmonary vascular mineralisation and significantly increased incidence of minimal alveolar histiocytosis (increased immune cell accumulation). These were not associated with other changes in the lungs, and were considered to be a compensatory response to inhalation exposure (Government of Canada, 2008; SCCS, 2010; HSDB; REACH).

Skin Irritation

Based on the available data in rabbits and humans (see **Observation in humans** section), the chemical is not considered to be irritating to skin.

In a dermal irritation study (similar to OECD TG 404) in NZW rabbits (n = 3/sex), animals were exposed (semi-occlusively) to the neat chemical on shaved sites (intact or abraded) for 24 hours and observed up to 72 hours. There were no signs of erythema (redness) or oedema (swelling), and the animals continued to gain weight during the study (REACH).

In three other studies, rabbits were exposed to the chemical for 4 hours and no irritation was reported (REACH).

Eye Irritation

Based on the available data, the chemical is not considered to be an eye irritant.

In a standard Draize test (similar to OECD TG 405) in NZW rabbits (n = 3/sex), 0.1 mL neat chemical was instilled into the conjunctival sac of one eye and animals were observed up to 72 hours. There were no signs of irritation (SCCS, 2010; REACH).

There was no eye irritation observed in two other acute eye irritation studies in rabbits (REACH).

Observation in humans

In several human repeated insult patch tests (see **Sensitisation: Observation in humans** section), various commercial formulations (leave-on hair spray, deodorant or antiperspirant) containing the chemical at 55.8–90.4 % were applied to the back of subjects. No irritation or minimal irritation reactions were observed in the subjects (SCCS, 2010; Johnson et al., 2011).

Sensitisation

Skin Sensitisation

Based on the available data in guinea pigs and humans (see **Observation in humans** section), the chemical is not expected to be a skin sensitiser.

In a mouse local lymph node assay (LLNA) (similar to OECD TG 429), female CBA mice (n = 5) were exposed to the chemical at 0, 10, 50 or 100 % in acetone/olive oil (3:1 v/v) vehicle. The stimulation index (a measure of the proliferative response of lymph nodes by thymidine incorporation) was <1 in treated mice, indicating that sensitisation did not occur (REACH).

In three separate Magnusson-Kligman maximisation tests, guinea pigs were administered the chemical at 1–5 % intradermally (in a vehicle of paraffin oil or cottonseed oil or physiological saline) and neat via the epicutaneous route in the induction phase. Guinea pigs were then challenged with the chemical at 10 % and/or neat via the epicutaneous route. No skin responses were observed (SCCS, 2010; REACH).

In a Buehler test in guinea pigs (n = 5 control and 10 treated), the chemical was not sensitising when administered in a saline vehicle (REACH). No further details are available.

Observation in humans

Repeated insult patch test (RIPT) studies in human subjects did not elicit sensitisation responses (SCCS, 2010; Johnson et al., 2011). The SCCS (2010) considers this type of testing as unethical.

In two separate RIPT studies (n = 110 subjects per study), 0.2 mL of a leave-on hairspray product containing approximately 90 % of the chemical was applied (semi-occlusively) for 24 hours to the back, three times per week, for three weeks during the induction phase. Ten to 17 days after the last induction patch, subjects were challenged with the chemical for 24 hours, and observations made upon patch removal and 48 hours later. Hardly noticeable to mild, and hardly noticeable effects were reported in 22 and 15 subjects in each of the studies, respectively. The effects were not considered to be clinically relevant irritation or sensitisation reactions (Johnson et al., 2011).

In another two RIPT studies, 106 subjects aged 18–66 years (>96 % with self-reported sensitive skin) and 105 subjects aged 18–70 years were exposed to 0.2 mL of a deodorant or antiperspirant product, respectively, containing approximately 56 % of the chemical. For induction, the chemical was applied (occlusively) for 24 hours to the shoulder blade region, three times per week, for three weeks. Ten to 15 days after the last induction patch, subjects were challenged with the same deodorant or antiperspirant product for 24 hours, and observations made 24 and 48 hours later. No sensitisation reactions were reported in either study (Johnson et al., 2011).

In 50 subjects (n = 28 males and 22 females) exposed (occlusively) to 0.05 mL of the chemical (concentration not specified) for 24 hours, three times per week, for three weeks; and then challenged 12 days after the last application with 0.05 mL chemical (concentration not specified). No irritation or sensitisation reactions were noted (SCCS, 2010).

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not considered to cause serious health effects from repeated oral exposure. Liver hypertrophy (enlargement) was consistently observed in the rat studies. The mechanism of action (MOA) for this effect may be similar to that induced by phenobarbital (PB), which is deemed to be not relevant for human health (Elcombe et al., 2014).

In a repeated dose toxicity study (OECD TG 408) in Wistar rats (n = 10/sex/dose), animals were administered the chemical by oral gavage at 0, 100, 330 or 1000 mg/kg bw/day for 13 weeks. Liver weights were significantly increased by 42–62 % in females exposed at ≥100 mg/kg bw/day compared with controls. This was not considered to be an adverse health effect, as there were no histopathological changes associated with the increased liver weights (Government of Canada, 2008; EA, 2009; SCCS, 2010; Dekant & Klaunig, 2016; REACH).

In a 28-day repeated dose toxicity study (similar to OECD TG 407) in SD rats (n = 6/sex/dose) that were administered the chemical at 0 or 1500 mg/kg bw/day, five days per week; liver weight was significantly increased in the treated female group compared with controls, but there were no gross pathological changes in liver (or other organs) (SCCS, 2010; Johnson et al., 2011; REACH).

In a repeated dose toxicity study (similar to OECD TG 407), SD rats (n = 8/sex/dose) were administered the chemical by oral gavage at 0, 25, 100, 400 or 1600 mg/kg bw/day, five days per week, for 14 days. Liver weights were significantly increased by 34–50 % in females exposed at ≥100 mg/kg bw/day compared with controls. Liver weights were also slightly increased in females exposed at 25 mg/kg bw/day (by 13 %) and males exposed at 1600 mg/kg bw/day (by 15 %). Similar to the 90-day study described above, it was reported that the liver effect was an adaptive response (EA, 2009; SCCS, 2010; Johnson et al., 2011; REACH).

In two mechanistic studies examining the potential relationship between the observed treatment-specific liver hypertrophy observed and hepatic enzyme induction, rats were administered the chemical by oral gavage at up to 2000 mg/kg bw/day for 4–12 days. Both studies also used PB as a positive control (for its ability to induce enzyme expression with resulting liver enlargement), administering it to a separate group of rats by intraperitoneal (i.p.) injection at 50 mg/kg bw/day. Increased liver weights were observed with chemical and PB exposure, and it was reported that the patterns of liver enzyme induction were similar between the two treatments (Government of Canada, 2008; EA, 2009; SCCS, 2010; Johnson et al., 2011; Dekant & Klaunig, 2016; HSDB; REACH). However, qualitative differences (e.g. increased responsiveness to the chemical in female rats, versus

increased responsiveness to PB in male rats) may reflect mechanistic differences in liver enzyme induction. It is therefore unclear whether the liver weight changes are adaptive or adverse effects (Government of Canada, 2008; Johnson et al., 2011; Franzen et al., 2016).

Dermal

Based on the available data, the chemical is not considered to cause serious health effects from repeated dermal exposure.

In a 28-day repeated dose dermal toxicity study (similar to OECD TG 410), SD rats (n = 10/sex/dose) were exposed (occlusively) to the chemical on shaved skin at 0, 200, 800 or 1600 mg/kg bw/day for six hours per day. Urinalysis confirmed that the chemical was absorbed and metabolised; no statistically or biologically significant local or systemic toxicity effects were reported (Government of Canada, 2008; EA, 2009; SCCS, 2010; Johnson et al., 2011; REACH).

In two other repeated dose dermal toxicity studies (according or similar to OECD TG 410) in NZW rabbits exposed to the chemical at 0, 96, 288 or 960 mg/kg bw/day five days per week for 21 days or at 0 or 1000 mg/kg bw/day seven days per week for 21 days, there were no signs of local or systemic toxicity (EA, 2009; SCCS, 2010; REACH).

Inhalation

Based on the available data, the chemical is not considered to cause serious health effects from repeated inhalation exposure, at concentrations up to the maximum reproducible vapour pressure of approximately 160 ppm. The MOA for the observed liver hypertrophy in rats may be similar to that induced by phenobarbital, which is deemed to be not relevant for human health (Elcombe et al., 2014).

In a combined chronic toxicity/carcinogenicity study (according to EPA OPPTS 870.4300), F344 rats were exposed (whole body) to the chemical vapour at: 0, 10, 40 or 160 ppm (0, 150, 600 and 2420 mg/m^3) for six hours per day, five days per week for 26 weeks (n = 6/sex/dose); 52 weeks (n = 10/sex/dose); 52 weeks followed by a 52 week recovery period (n = 20/sex/dose); or 106 weeks (n = 60/sex/dose) (see **Carcinogenicity** section for results from the last group). The no observed adverse effect concentration (NOAEC) was ≥160 ppm. Mortality in the recovery group (rats exposed for 52 weeks, followed by a 52 week recovery period) ranged from 15–75 % for males and 5–30 % for females. There was a significant positive trend in mortality for males with increasing exposure concentration. Body weight was similar in all groups, irrespective of the treatment regimen. There was an increased incidence of hyaline inclusions in the nasal olfactory epithelium of rats exposed to the highest concentration in all treatment regimens; females were more affected than males. The hyaline inclusions were not associated with overt inflammatory responses or tissue damage. Red blood cell count was reduced in males exposed at ≥40 ppm for 26 weeks, but changes were deemed minimal and there was no evidence of increased haematopoiesis. Liver weights were significantly increased in females exposed to the chemical for 26 or 52 weeks, but not in a concentration- or time-dependent manner. The liver weight changes were associated with altered serum metabolic parameters including decreased urea concentration, increased cholesterol, increased triglyceride, and increased gamma glutamyl transferase following 52 weeks' exposure (US EPA, 2005; Government of Canada, 2008; EA, 2009; SCCS, 2010; Dekant & Klaunig, 2016; Jean et al., 2016; REACH).

In a repeated dose inhalation toxicity study (OECD TG 413), F344 rats (n = 20/sex/dose) were exposed (nose only) to the chemical vapour at 0, 26, 46, 86 or 224 ppm (0, 441, 758, 1351 and 3591 mg/m^3) for six hours per day, five days per week for three months. Animals were euthanised at the end of the three months; or, for separate groups of rats (n = 10/sex/dose) exposed at 0 or 224 ppm, after an additional 28-day recovery period. There were no effects on body weight, food intake, survival or urinalysis parameters. The NOAEC was 26 ppm based on liver weights that were significantly increased in males at the highest dose and in females at doses ≥46 ppm, with changes reversed during the recovery period. Observations in the liver were not accompanied by histopathological changes. Serum gamma glutamyl transferase (an enzyme that may indicate liver impairment) was increased in males exposed at the highest dose, and in females in a dose-dependent manner at ≥46 ppm; the effect in females did not reverse during the recovery phase. Serum lactate dehydrogenase (an enzyme that may indicate tissue damage) was decreased in females at ≥86 ppm and did not reverse during the recovery phase. Lung weights increased in a dose-dependent manner and were significantly increased in rats exposed at 224 ppm; this resolved in the males, but not in the females, during the recovery period. Lung macrophage accumulation and alveolitis (interstitial inflammation) were observed in animals exposed at doses ≥86 ppm, but the incidence and severity of these changes were considered similar to spontaneous changes occurring in control animals following nose-only exposures. In females exposed at the highest dose, there was an increased incidence of ovarian interstitial gland hyperplasia, vaginal mucification and atrophy, and changes in the mammary gland; the vaginal changes persisted even after the recovery period (Government of Canada, 2008; EA, 2009; SCCS, 2010; Johnson et al., 2011; Danish EPA, 2014; Dekant & Klaunig, 2016; HSDB; REACH).

In a 90-day repeated dose inhalation toxicity study (conducted similarly to OECD TG 413), SD rats (n = 10/sex/dose) were exposed (whole body) to the chemical vapour at 0, 20, 60 or 120 ppm for six hours per day, seven days per week for 90 days. Animals were euthanised at the end of the 90 days; or, for separate groups of rats (n = 10/sex/dose) exposed at 0 or 120 ppm, after an additional 28-day recovery period. The only systemic effect observed was significantly increased relative liver weight in females at the highest dose, which was reversed during the recovery period (SCCS, 2010; Johnson et al., 2011; Danish EPA, 2014; Dekant & Klaunig, 2016; REACH).

In a repeated dose inhalation toxicity study (OECD TG 412), F344 rats (n = 25/sex/dose) were exposed (whole body) to the chemical vapour at 0, 10, 25, 75 or 160 ppm (0, 154, 385, 1156 and 2466 mg/m^3) for six hours per day, seven days per week for 28 days. Animals were euthanised at the end of the 28-day period, or after a 14-day recovery period. There were no effects on body weight, food intake, survival, urinalysis, haematological or ophthalmological parameters. The only systemic effects observed were at 160 ppm, where there were increased liver and lung weights, and increased lung alveolar macrophage accumulation compared with control rats. All effects were reversed during the recovery phase (Government of Canada, 2008; EA, 2009; SCCS, 2010; Johnson et al., 2011; Danish EPA, 2014; Dekant & Klaunig, 2016; HSDB; REACH).

In other 28-day repeated dose inhalation toxicity studies (conducted similarly to OECD TG 412), rats were exposed to the chemical vapour at up to approximately 2500 mg/m^3 or to the chemical aerosol at approximately 3060 mg/m^3. The only systemic effects were increased liver weights, liver cell hypertrophy and haematological changes (that were not considered to be treatment-related) in treated rats compared with control rats (SCCS, 2010; Johnson et al., 2011; Danish EPA, 2014; Dekant & Klaunig, 2016; REACH).

In a mechanistic study examining the relationship between the observed liver hypertrophy and liver enzyme induction, female F344 rats (numbers not specified) were exposed to the chemical vapour at 0 or 160 ppm for six hours per day, five days per week for 28 days; a subset of animals was also examined after a 14-day recovery period. Treatment with PB (dose not specified) was used as a positive control in a separate group of rats. Liver weight in chemical-treated rats was significantly increased by 16 % compared with controls, and this effect was reversed during the recovery period. Changes in the profile of liver microsomal enzymes were qualitatively similar between rats exposed to the chemical and PB, suggesting a similar MOA (Government of Canada, 2008; EA, 2009; SCCS, 2010; Dekant & Klaunig, 2016; HSDB; REACH). Given the transient nature of some of the liver changes in this study and other studies as reported above, the liver effects are considered adaptive responses to the chemical (Government of Canada, 2008; Johnson et al., 2011; Franzen et al., 2016).

Genotoxicity

Based on the available data, the chemical is not considered to be genotoxic.

The chemical gave negative results in the following in vitro tests (Government of Canada, 2008; EA, 2009; SCCS, 2010; Johnson et al., 2011; Dekant & Klaunig, 2016; REACH):

- several bacterial reverse mutation assays (according or similar to OECD TG 471) in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538, and *Escherichia coli* WP2 uvrA strain, exposed to the chemical at up to 12 500 µg/plate or up to 500 µL/plate, with and without metabolic activation;
- a bacterial DNA repair assay (similar to EPA OPPTS 870.5500) in *E. coli* polA+ strain exposed to the chemical at up to 5 mg/plate, with and without metabolic activation;
- a DNA damage and mitotic recombination assay in *Saccharomyces cerevisiae* exposed to the chemical at up to 5 µL/plate, with and without metabolic activation;
- two mammalian chromosome aberration tests (according or similar to OECD TG 473) in Chinese hamster lung fibroblasts (V79) and mouse lymphoma (L5178Y) cells exposed to the chemical at up to 25 µL/mL, with and without metabolic activation;
- a mammalian cell gene mutation assay (similar to OECD TG 476) in L5178Y cells exposed to the chemical at 0.8–12.5 µL/mL, with and without metabolic activation; and
- DNA damage and/or repair assays (sister chromatid exchange, unscheduled DNA synthesis (UDS) and alkaline elution) in L5178Y cells exposed to the chemical at up to 25 µL/mL, with and without metabolic activation.

The chemical gave negative results in the following in vivo tests (Government of Canada, 2008; EA, 2009; SCCS, 2010; Johnson et al., 2011; Dekant & Klaunig, 2016; REACH):

- a UDS assay (OECD TG 486) in hepatocytes from F344 rats (n = 6/sex/dose) exposed (whole body) to the chemical vapour at 0 or 160 ppm for six hours per day for seven consecutive days; and
- a mammalian erythrocyte micronucleus test (OECD TG 474) in bone marrow cells from F344 rats exposed (whole body) to the chemical vapour at 0 or 160 ppm for six hours per day for seven consecutive days.

Carcinogenicity

The chemical shows potential for carcinogenicity in female rats only, potentially by a mechanism that is not considered relevant to humans. Based on the available data, and MOA analysis for the observed tumours, the chemical is not considered to be carcinogenic.

In a previously described (see **Repeat dose toxicity: Inhalation** section) combined chronic toxicity/carcinogenicity study, F344 rats were exposed (whole body) to the chemical vapour at 0, 10, 40 or 160 ppm for six hours per day, five days per week for 106 weeks (n = 60/sex/dose). There were no treatment-related effects on survival, body weight, ophthalmological parameters, haematology, clinical chemistry and urinalysis parameters in any of the groups. Non-neoplastic changes included increased incidence of hyaline inclusions in the nasal olfactory epithelium and increased liver weights at the highest concentration only. In females exposed to the highest concentration, there was a significantly increased incidence of endometrial adenocarcinoma. Endometrial adenomatous polyps and endometrial adenocarcinoma were also increased in females from the recovery group. Obligatory preceding lesions to these uterine neoplasms were not observed in these animals, e.g. uterine adenoma or endometrial hyperplasia (US EPA, 2005; Government of Canada, 2008; EA, 2009; SCCS, 2010; Johnson et al., 2011; Danish EPA, 2014; Dekant & Klaunig, 2016; Franzen et al., 2016; Jean et al., 2016; REACH).

The mechanism by which the endometrial adenocarcinomas occur in F344 rats may be related to dopamine agonist activity of the chemical, leading to hormonal dysregulation that can stimulate the development and progression of these tumours. This MOA is mediated via the hypothalamus in rats, and occurs in a manner that is not considered plausible in humans due to species differences in hormonal regulation (Jean et al., 2016; Klaunig et al., 2016).

Reproductive and Developmental Toxicity

Based on the available data, the chemical is not considered to cause reproductive or developmental toxicity following inhalation exposure at concentrations up to the maximum reproducible vapour pressure of approximately 160 ppm.

In a dose-finding one-generation reproductive toxicity study, SD rats (n = 22/sex/dose) were exposed (whole body) to the chemical vapour at 0, 26 or 132 ppm (0, 401 and 2034 mg/m^3) for six hours per day, seven days per week, for four weeks prior to mating and until the end of breeding for parental males, until postnatal day (PND) 21 for parental females and until PND 28 for pups. Pregnant females were not exposed to the chemical from gestation day (GD) 21 to lactation day 4. There were no adverse effects of chemical exposure on parental body weight, food intake and reproductive parameters —including fertility, mating, average number of implantation sites, gestation, pup delivery and live litter size. In two dams exposed to the highest dose, there was total litter loss; this was not investigated further. Pups were otherwise unaffected by chemical exposure in terms of average body weight, sex ratios and viability (EA, 2009; SCCS, 2010; Johnson et al., 2011; Danish EPA, 2014; Dekant & Klaunig, 2016; REACH).

In a two-generation combined reproductive toxicity (according to EPA OPPTS 870.3800) and developmental neurotoxicity (according to EPA OPPTS 83-6) study, SD rats (n = 30/sex/dose) were exposed (whole body) to the chemical vapour at 0, 30, 70 or 160 ppm (0, 478, 1094 and 2496 mg/m^3) for six hours per day, seven days per week, for 70 days prior to mating and up to PND 70 depending on the stage of the study. Pregnant females were not exposed to the chemical from GD 21 to lactation day 4; and second generation (F2) offspring were not exposed to the chemical directly. Overall, there was no evidence of parental toxicity, reproductive toxicity, neonatal toxicity, or developmental neurotoxicity. There was no difference in body weight, food intake, organ weight, survival, mating indices, fertility indices (including number of corpora lutea, ovarian primordial follicle counts, sperm counts, sperm motility and sperm morphology), pregnancy rate, pregnancy duration and delivery between groups of initial generation (F0) and first generation (F1) parental animals. In one F0 female exposed to the highest dose, a single pup was delivered and did not survive, but this was not considered to be treatment-related. For offspring F1 and F2 animals, litter size, average body weights, pup viability, sex ratios and developmental markers of puberty were similar between all groups. Neurodevelopment in the F2 offspring was not affected by parental chemical exposure, as assessed by motor activity, startle response, spatial learning (using the Biel water maze) and neurotoxicity screening (using the functional observational battery) (Government of Canada, 2008; EA, 2009; SCCS, 2010; Danish EPA, 2014; Dekant & Klaunig, 2016; HSDB; REACH).

Other Health Effects

Endocrine Disruption

In vitro

The chemical did not bind to human oestrogen receptors (ER) a or β, nor did it stimulate the expression of oestrogen in human epithelial (MCF-7) cells. The chemical did not bind to progesterone receptors a or β (Government of Canada, 2008; SCCS, 2010; Johnson et al., 2011; Dekant & Klaunig, 2016; REACH).

In vivo

The chemical did not show oestrogenic or anti-oestrogenic activity in two separate in vivo rat uterotrophic assays, where animals were exposed to the chemical by inhalation (whole body) at 160 ppm for 16 hours per day, for three days. No oestrogenic activity was observed in various mouse models (including ERa knockout mice and ovariectomised mice) that were orally exposed to the chemical at up to 1000 mg/kg bw. The chemical did not show androgenic or anti-androgenic activity in a Hershberger assay in rats exposed to the chemical by inhalation (whole body) at 160 ppm for 16 hours per day, for 10 days (SCCS, 2010; Johnson et al., 2011; Dekant & Klaunig, 2016; REACH).

Risk Characterisation

Critical Health Effects

There are no critical health effects for the chemical.

The liver hypertrophy and endometrial adenocarcinoma observed in rats following repeated oral and/or inhalation exposure occur by mechanisms not considered to be relevant to humans.

Public Risk Characterisation

Considering the range of cosmetic and domestic products that may contain the chemical, the main route of public exposure is expected to be through the skin, inhalation from products applied as aerosols, and incidental oral exposure. Industry (Franzen et al., 2016), the European Commission SCCS opinion on decamethylcyclopentasiloxane (cyclopentasiloxane, D5) in cosmetic products (SCCS, 2015), the Cosmetic Ingredient Review Expert Panel (Johnson et al., 2011), the European Commission SCCS Opinion on Cyclomethicone: Octamethylcyclotetrasiloxane (Cyclotetrasiloxane, D4) and Decamethylcyclopentasiloxane (Cyclopentasiloxane, D5) (SCCS, 2010) and the Government of Canada (2008) reported derived margins of safety (MoS) or margins of exposure (MoE) from the wide dispersive use the chemical in cosmetics (and other scenarios) based on its health effects and

average concentrations in personal care products (and other consumer products). Overall, the MoS/MoE estimates indicate that the chemical, when used in consumer products, does not pose a human health risk. Hence, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

Workers may be exposed to the chemical during its production, formulation into consumer products (e.g. cosmetics and dry cleaning agents) or use in professional settings. Based on the derived MoS/MoE estimated for occupational exposure, the chemical is not likely pose an occupational health risk (Johnson et al., 2011; Franzen et al., 2016). Hence, the risk to workers from exposure to the chemical is not considered to be unreasonable.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required at this stage.

There is a current EU restriction proposal on the chemical in wash-off personal care products based on environmental concerns (see **Restrictions: International** section). If, during the REACH authorisation process, data become available which may affect the human health outcomes, further assessment may be required.

Regulatory Control

Work Health and Safety

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction. Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals— Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemicals has not been undertaken as part of this assessment.

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